AD-A137 692 BLOOD VISCOSITY CHANGES FOLLOWING SURGICAL STRESS AND TRAUMA(U) TULANE UNIV NEW ORLEANS LA SCHOOL OF MEDICINE M S LITWIN JAN 80 DADA17-67-C-7049 1/1

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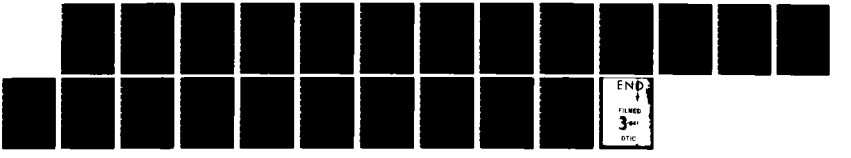

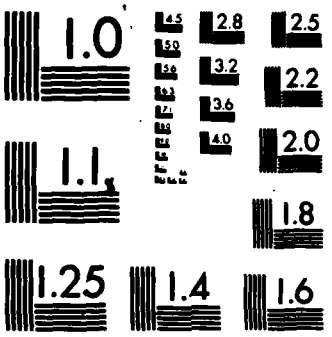

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REPORT NO. 10

BLOOD VISCOSITY CHANGES FOLLOWING SURGICAL STRESS AND TRAUMA

FINAL PROGRESS REPORT

by

MARTIN S. LITWIN, M.D.

JANUARY, 1980

SUPPORTED BY

U.S. ARMY MEDICAL RESEARCH AND DEVELOPMENT COMMAND

WASHINGTON, D.C. 20314

CONTRACT NO. DADA17-67-C-7049

TULANE UNIVERSITY MEDICAL SCHOOL

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REPORT DOCUMENTATION PAGE

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1. REPORT NUMBER	2. GOVT ACCESSION NO. AD-A137692 / 3. RECIPIENT'S CATALOG NUMBER
4. TITLE *(and Subtitle)* BLOOD VISCOSITY CHANGES FOLLOWING SURGICAL STRESS AND TRAUMA	5. TYPE OF REPORT & PERIOD COVERED Final Report January 1980
	6. PERFORMING ORG. REPORT NUMBER
7. AUTHOR(s) Martin S. Litwin, M.D.	8. CONTRACT OR GRANT NUMBER(s) DADA17-67-C-7049
9. PERFORMING ORGANIZATION NAME AND ADDRESS Tulane University Medical School New Orleans, Louisiana 70112	10. PROGRAM ELEMENT, PROJECT, TASK AREA & WORK UNIT NUMBERS 61102A.3M161102BS02.00.001
11. CONTROLLING OFFICE NAME AND ADDRESS US Army Medical Research and Development Command Fort Detrick Frederick, Maryland 21701	12. REPORT DATE January 1980
	13. NUMBER OF PAGES 22
14. MONITORING AGENCY NAME & ADDRESS*(if different from Controlling Office)*	15. SECURITY CLASS. *(of this report)* Unclassified
	15a. DECLASSIFICATION/DOWNGRADING SCHEDULE

16. DISTRIBUTION STATEMENT *(of this Report)*

This document has been approved for public release and sale; its distribution is unlimited.

17. DISTRIBUTION STATEMENT *(of the abstract entered in Block 20, if different from Report)*

18. SUPPLEMENTARY NOTES

19. KEY WORDS *(Continue on reverse side if necessary and identify by block number)*

20. ABSTRACT *(Continue on reverse side if necessary and identify by block number)*

DD FORM 1 JAN 73 1473 EDITION OF 1 NOV 65 IS OBSOLETE

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Foreword

In conducting the animal research described in this report, the investigators adhered to the "Guide for Laboratory Animal Facilities and Care," as promulgated by the Committee on the Guide for Laboratory Animal Resources, National Academy of Sciences - National Research Council.

FINAL PROGRESS REPORT

Principal Investigator: Martin S. Litwin, M.D.

I. TYPE OF PROPOSED STUDY

Definitive Study

II. SPECIFIC AIMS

A. To define the types of whole blood, plasma and packed cell viscosity changes occurring following surgical stress and trauma, to relate these changes to metabolic derangements associated with such states, and to define the effects of cellular aggregation and disaggregation on these variables.

B. To serve as testing laboratory for Surgical Division, U.S. Army Medical Research and Development Command, in evaluation of metabolic and blood physico-chemical effects of plasma expanders.

C. To determine the role of pulmonary microembolism associated with massive blood transfusion in development of pulmonary insufficiency.

III. PROGRESS UNDER THIS CONTRACT

A. Effect of New Plasma Expanders:

At the request of the Surgical Research Branch, U.S. Army Medical Research and Development Command, infusion of PAMEG and colloidal hemoglobin solution into the anaesthetized, otherwise normal animals, was carried out and effects on blood physico-chemical changes followed.

1. PAMEG: Once constant baseline levels had been attained, 500 cc PAMEG in normal saline or 500 cc colloidal hemoglobin solution was infused over two hours into dogs on constant respiration. Measurements were made prior to infusion, one hour after infusion had been started, at the end of infusion, and one and two hours respectively after infusion had been completed.

In those animals infused with PAMEG there was a moderate increase in whole blood viscosity and a marked increase in packed cell viscosity even though hematocrit dropped an average of 7%. Arterial pH and pCO_2 remained constant while pO_2 rose continuously through the experimental period. O_2 consumption dropped an average of 2 cc/kg/minute. Arterial blood lactate dropped an average of 1.3 mg% while pyruvate dropped an average of 2.8 mg%. When PAMEG was infused as delivered, marked hemolysis was noted. This was considerably lessened on dilution with normal saline, but mild hemolysis was still noted. On observation of the conjunctival small vessel circulation there was red cell aggregation and stasis of blood flow in small arterioles and venules.

2. Stroma-free Colloidal Hemoglobin Solution: On infusion of hemoglobin solution, hematocrit dropped an average of 10%; whole blood viscosity went down an average of 2.6 cps at 23 sec^{-1} and packed cell viscosity went down an average of 11 cps at 23 sec^{-1}. Plasma viscosity in the PAMEG group increased while that in the colloidal hemoglobin group remained essentially constant. Arterial pH and pCO_2 remained constant while pO_2 rose. O_2 consumption remained essentially constant. Lactate rose an average of 3 mg% and pyruvate an average of 0.4 mg%, but both returned to normal levels by two hours after infusion had been completed.

In both sets of experiments total protein concentration rose markedly. This was undoubtedly a manifestation of the protein nature of the material infused. Fibrinogen concentration dropped consistently but this drop appeared to be dilutional since the magnitude of the decreases noted were identical in both groups and in controls.

As a result of these preliminary experiments, our laboratories were directed to conduct a major research effort into the renal effects of stroma-free hemoglobin.

a. Renal clearance of stroma-free hemoglobin

Rabiner and colleagues introduced a hemoglobin solution free of not only stroma but also lipid, a stromal contaminant and our preliminary experiments indicated that this material was not nephrotoxic to the dog. The present study was undertaken to determine plasma persistence, renal clearance, and urinary excretion of this same material infused into normal dogs.

Normal female dogs were infused with hemoglobin solution which was free of stroma and lipid contaminants. Animals were killed at the conclusion of the experiments, and the liver, lungs, and kidneys examined for pathologic changes.

Renal function tests and histologic examinations failed to demonstrate that the solution was toxic to the kidneys, liver, or lungs in normal dogs. The urine pH of all animals was constantly above pH 6, and there was no spectrophotometric evidence of toxic breakdown products of hemoglobin in the urine of any animal.

During the first six hours after infusion, 60 percent of the total amount of hemoglobin infused was excreted in the urine, and an additional 7 per cent was excreted during the subsequent 18 hours. By 24 hours after infusion, plasma hemoglobin levels had dropped below the hemoglobin-binding capacity of the plasma, and hemoglobin had disappeared from the urine.

The effects on the reticuloendothelial system, on renal function after trauma and in the presence of an acid urine, and on oxygen consumption, and antigenicity, were not studied.

b. Effect of acidosis on renal clearance of stroma-free hemoglobin

In experiments on dogs, hemoglobinemia and hemoglobinuria in the presence of a metabolic acidosis and an acid urine have been implicated in the development of hemoglobinuric nephrosis and acute tubular necrosis. In addition, metabolic acidosis and a drop in urine pH commonly occur after trauma, hemorrhage, or surgical insult, and it is in these latter situations that a hemoglobin plasma expander most likely would be of use. For these reasons, the present study was undertaken to determine the renal effects and clearance of stroma-free hemoglobin solution in acidotic dogs.

Metabolic acidosis with an acid urine was induced in two groups of dogs by the administration of ammonium chloride. Those dogs used as controls were then infused with normal saline solution and those used for the experiment were infused with a stroma-free hemoglobin solution. As determined by renal function tests, stroma-free hemoglobin was not nephrotoxic in acidotic dogs. Hemoglobin infusion caused an increase in urine volume and pH during the first two hours after infusion.

Immediately after hemoglobin infusion, mean plasma hemoglobin concentration was 1.8 ± 0.2 gram per cent; 24 hours later, it had decreased to 68 ± 24 milligrams per cent. During the first six hours after infusion, 47 per cent of the hemoglobin infused was excreted in the urine; an additional 14 per cent was excreted during the subsequent 18 hours. The methemoglobin fraction of the excreted hemoglobin pigment was approximately 20 to 30 per cent greater than that in the infused solution. Histologic examination of lungs, livers, and kidneys and repeated urinalyses demonstrated no differences between the dogs used as controls and those infused with hemoglobin.

c. Effect of renal ischemia on clearance of stroma-free hemoglobin

Another study was undertaken to define the renal effects and clearance of stroma-free hemoglobin after an episode of renal ischemia. A modification of an experimental animal preparation developed previously for the study of nephrotoxicity of heme-containing compounds was utilized.

Right nephrectomy, left renal explantation to a subcutaneous position and placement of a renal artery snare were performed on each of 12 female dogs. After a recovery period of at least 2 weeks and when renal function was determined to be normal, six control animals were infused with normal saline after renal artery snares were tightened. Six other animals treated similarly were infused with stroma-free hemoglobin solution. Renal biopsies were taken before renal ischemia and 6 hours and 48 hours after ischemia. Animals were sacrificed 5 days after infusion and the kidneys, liver, and lungs examined.

As determined by renal function tests, stroma-free hemoglobin solution was not toxic to the ischemic canine kidney under the conditions of this experiment. The pH of the animals remained at or above 6.9 during the first 24 hours after hemoglobin infusion, and there was no spectrophotometric evidence of toxic breakdown products of hemoglobin in the urine of any animal.

During the initial 6 hours after hemoglobin infusion and removal of the snare, average plasma hemoglobin concentration decreased from 1.5 $\pm$ 0.8 Gm./100 ml. to 0.32 $\pm$ 0.17 Gm./100 ml. Twenty-four hours after infustion, plasma hemoglobin concentration was 45 $\pm$ 80 mg./100 ml. Forty-one per cent of the infused hemoglobin was recovered in the urine, 28% during the initial six hours and an additional 13% during the succeeding 18 hours. After 24 hours urinary hemoglobin could no longer be demonstrated.

Repeated urinalysis and histologic examinations of renal tissues taken before infusion and 6 hours, 48 hours and 5 days after renal artery occlusion and infusion demonstrated no essential differences between the kidneys of control dogs infused with saline and those infused with the hemoglobin solution.

B. Metabolic Effects of Experimental Anaesthesia:

As an outgrowth of animal experiments, further research was accomplished to define the metabolic effects of the anaesthetics used in our animal research.

1. Pentobarbital: Even though pentobarbital anaesthesia is widely used in surgical experiments, its effects on total body O_2 consumption and on lactate and pyruvate metabolism have not been investigated. The purpose of this study was to determine cardiovascular and metabolic changes caused by pentobarbital intoxication in the ventilated dog so that further insight might be gained into the effect of this material on similar observations made during surgical experiments.

Dogs were anaesthetized initially with intravenous sodium pentobarbital, 35 mg/kg, and further increments of 8 mg/kg were given intravenously at the end of each experiment. All animals were ventilated with room air on a Harvard respirator. Under fluoroscopy a number 3 French teflon radiopaque catheter was inserted through the right jugular vein and its tip placed into the pulmonary artery. A vinyl catheter with a 3-way stopcock was inserted into the femoral artery and attached to a pressure transducer. This transducer was used to record arterial blood pressure and pulse rate. Esophageal and skin temperature were monitored by a telethermometer and total body O_2 consumption was measured with a continuous O_2 consumption analyzer. Cardiac output was measured by the direct Fick method.

Average initial blood barbiturate concentrate was 4.1 mg%; this increased by 51% over a 4½ hour period due to additional intravenous injections of 8 mg/kg.

The depressant effects of the drug caused a marked decrease by 50% in cardiac output; pulse rate and pulse pressure were reduced by 35% and 51% respectively. Esophageal temperature progressively declined from 37.2°C to 33.0°C and total body O_2 consumption progressively decreased by 44% from an initial high of 6.6 ml/kg/min. to 3.7 ml/kg/min. Blood lactate and pyruvate concentrations decreased during the experiment indicating depressed glycolysis in face of an adequate tissue perfusion and oxygenation.

O_2 consumption and cardiac output tended towards stabilization after 2½ hours despite further increases in serum pentobarbital concentration. Skin and esophageal temperature showed a similar tendency but to a lesser degree.

It was concluded from these experiments that pentobarbital anaesthesia causes marked alterations in tissue metabolism and is therefore an unsatisfactory anaesthetic agent for use in surgical experiments.

2. Morphine: Ideally anaesthetics used in experimental surgery should be free of cardiovascular and metabolic side effects. Avoidance of such effects is particularly desirable in the study of cardiovascular physiology. In other experiments barbiturates were shown to cause both cardiovascular and metabolic depression in the dog. This study was undertaken to determine the circulatory and metabolic effects caused by morphine when used to produce deep and prolonged anaesthesia in dogs.

Normal dogs were given morphine 3 mg/kg body weight intravenously. They were then given a further dose of intravenous morphine, 5 to 7 mg/kg until deeply anaesthetized. Tubocurare, 1.5 mg/kg was given intravenously and an endotracheal tube inserted. Animals were ventilated with room air using a Harvard respirator at a rate and volume which were regulated so as to maintain arterial pH, pCO_2 and pO_2 at normal levels.

Cardiac output was measured by the direct Fick method after inserting a Teflon radiopaque catheter through the right jugular vein into the pulmonary artery. A vinyl catheter with a 3-way stopcock was inserted into the femoral artery and attached to a pressure transducer; this was used to record arterial pulse and blood pressure. Esophageal and skin temperatures were measured by a telythermometer and total body O_2 consumption using a continuous O_2 consumption analyzer. Total peripheral resistance and mean arterial pressure were calculated using standard formulas. Observations were made at approximately hourly intervals. During the experimental period of 4½ hours there was no evidence of circulatory or metabolic depression in any animal. Mean arterial blood pressure, total peripheral resistance, pulse rate and cardiac index remained within normal limits. The only detectable trend toward change was in the arterial pressure which tended to rise slightly. O_2 consumption and temperature were stable throughout, and arterial pH, pCO_2, and pO_2 were maintained within normal limits.

It was concluded from these experiments that deep morphine anaesthesia is better than pentothal anaesthesia for use in surgical physiological experiments. It appears to cause minimal interference with cardiovascular and metabolic processes; however, prolonged respiratory depression following completion of the experiment necessitates continued artificial respiration. Morphine antidotes were not utilized in these experiments.

3. Oxygen Consumption After Hyperventilation: As a part of this extended investigation into the metabolic and vascular effects of trauma and in order to define changes due to a difference in oxygen availability, O_2 consumption was determined at intervals before, during, and after a hyperventilatory episode in dogs. It was found during our investigation under this contract last year that passive hyperventilation of anaesthetized dogs on room air caused a dramatic increase in whole body O_2 consumption which could not be explained on the basis of increased muscular effort. Each animal developed an increased uptake of oxygen with the inception of hyperventilation; this passed away concurrent with termination of that hyperventilation. Huckabee in his often quoted experiments (J. Clin. Invest., 37:244-254, 255-263, and 264-271, 1958) was unable to demonstrate any change in whole body oxygen requirements by utilizing "excess lactate" to express oxygen debt and increased consumption.

In the present experiments when animals were subjected to prolonged forced hyperventilation, O_2 consumption went up an average of 11.1 cc per minute per kilo during the hyperventilatory episode. Following hyperventilation the O_2 consumption decreased below normal control levels an average of 1 cc per minute per kilo. Lactate:pyruvate changed considerably. Lactate went up an average of only 6 mg% while pyruvate went up 1.2mg%.

Certainly there was no O_2 debt that developed in our animals during hyperventilation; however, this was undoubtedly due to the ready availability of large amounts of oxygen stored both in the hemoglobin and the myoglobin. This readily available oxygen allowed lactate which accumulated to be converted almost immediately to pyruvate. Pyruvate thus rose out of proportion to lactate and lactate:pyruvate decreased markedly.

To study the effect of carbon dioxide on this phenomenon a series of animals were hyperventilated with 95% oxygen:5% carbon dioxide. Oxygen consumption again rose an average of 9 cc per minute per kilo. pH remained constant while pCO_2 climbed markedly to 530 mmHg. Lactate and pyruvate both rose to approximately double their control concentrations.

C. Human Blood Viscosity:

This research was performed to define changes in blood viscosity after trauma and to relate these changes to physiologic and metabolic derangements.

1. Normal Blood Viscosity: It was the purpose of this investigation to define blood viscosity range in the normal human and to correlate these standards with other parameters known to be of importance in the determination of blood viscosity.

Whole blood (WB), packed cell (PC), and plasma (P) viscosities and various parameters in blood felt to be most influential in these determinations have been measured in 50 normal adult human subjects. Average normal WB viscosity at 23 sec^{-1} was 6.7 cps (S.D. $\pm$ 1.1) for the composite group, 7.0 cps (S.D. $\pm$ 0.9) for the men, and 5.5 cps (S.D. $\pm$ 0.6) for the women. Average PC viscosity at the same shear rate was 85.2 cps (SD $\pm$ 7.5) for the composite sample, 86.1 cps (S.D.) $\pm$ 8.0) for the men, and 82.5 cps (S.D.) $\pm$ 7.1) for the women. Average P viscosity at 230 $sec.^{-1}$ was 1.4 cps (S.D. $\pm$ 0.1) for the composite group, for the men, and for the women.

2. Physical Variables: Further experiments were performed to illustrate the relationship between hematocrit and whole blood viscosity in the normal human and to determine the influence on normal human whole blood viscosity of temperature of the blood and length of time on standing in vitro.

Normal human blood viscosity at an hematocrit of 36% was only one-half the blood viscosity noted when hematocrit was 53%. Whole blood viscosity determined at 37.5°C. was markedly less than whole blood viscosity of the same blood when determined at 25°C. Marked fluctuations in viscosity were noted when blood was allowed to remain in vitro for long periods of time prior to viscosity determinations.

3. Effect of Surgical Trauma in Animals: In the present research, red cell aggregation was induced in dogs by a severe surgical operation. Animals were then infused with dextran 70 or dextran 40, and various physiologic parameters were studied. It was the purpose of this study to define the metabolic effects of disaggregation produced by dextran 40 infusion in the postoperative period and to define and compare the metabolic effects of dextran 70 and dextran 40 in postoperative animals.

A severe surgical operation was performed on dogs, and each was then infused with normal saline, dextran 70, or dextran 40. Various parameters were studied before and immediately after operation, and prior to, during, and after infusion. In all animals after operation O_2 consumption dropped, whole blood (WB) and packed cell (PC) viscosities increased, and cellular aggregates were readily observed in the sluggish small vessel circulation. Following infusion marked drops in hematocrit levels were associated with decreases in whole blood (WB) viscosities.

In animals infused with normal saline, the O_2 consumption remained at low levels and PC viscosities progressively increased throughout the experiment; cellular aggregates persisted in the small vessel circulation. Similar changes noted after dextran 70 infusion were even more marked.

In contrast, O_2 consumption increased and PC viscosity decreased markedly after dextran 40 infusion. Cellular aggregates resolved and previously irregular stagnant flow through partially blocked small vessels became regular, rapid, and even; this smooth flow persisted until the end of the experimental period.

4. Effect of Surgical Trauma in Humans:

a. Physical effects

The effects of surgical operations on whole blood (WB) viscosity and several of its predeterminants were studied in 20 patients. Average WB viscosities were reduced postoperatively as a result of hemodilution. There were associated decreases in hematocrits and serum globulin and fibrinogen concentrations. When the dilution factor was eliminated, definite increases were noted postoperatively in average packed cell (PC) viscosities. Elimination of hematocrit as a variable in blood viscosity by using WB viscosity : hematocrit ratios for correlative analyses failed to demonstrate increased correlations postoperatively with average plasma total protein, albumin, globulin, or fibrinogen concentrations.

b. Metabolic effects

Experiments were then performed to confirm whether the increase in packed cell (PC) viscosity that occurs in humans after elective surgery is accompanied by a decrease in total body O_2 consumption as previously noted in animals, and further to define the effect of resolution of intravascular cellular aggregates (ICA) on these parameters. Thirty-nine patients were studied. Total body O_2 consumption was 76% of normal 6 hours postop, 81% of normal 24 hours postop and 87% of normal 48 hours postop. Twenty-four hours after operation PC viscosity had increased markedly. Saline infusion had no significant effect on total body O_2 consumption or PC viscosity, either pre- or postop, but WB viscosity decreased linearly in proportion to the drop in hematocrit. Resolution of ICA by dextran 40 infusion was associated with return of total body O_2 consumption and PC viscosity to normal; a decrease in WB viscosity was disproportionately greater than would have been seen had the decrease been due solely to the drop in hematocrit. It is concluded that in humans surgical trauma causes an increase in PC viscosity and microcirculatory impairment as evidenced by a decrease in total body O_2 consumption. Resolution of ICA by dextran 40 infusion reverses these detrimental changes.

5. Accuracy of Blood Fibrinogen Determinations: Studies were completed on the accuracy and reproductability of plasma fibrinogen determinations performed by different methods on blood samples from animals given dextran. These results indicated that the four accepted methods for determination of fibrinogen concentration in animals may vary as much as 500% when fibrinogen determinations are performed after infusion of dextran.

Rabbits were first immunized against pooled dog plasma. Then other pooled dog serum was reacted with calcium chloride to remove all traces of fibrinogen and other clotting factors. The fibrinogen free serum was reacted with serum from the immunized rabbits leaving antifibrinogen in solution. This rabbit dog-antifibrinogen was prepared in small quantities originally, and larger quantities suitable for laboratory research were readied.

When this antifibrinogen was mixed with whole plasma, a precipitant formed. When the same plasma had previously been mixed with dextran, this precipitation was much more marked indicating that some of the dextran was being pulled down with the fibrinogen. Presumably this represented coupled dextran.

Immunoelectrophoretic studies did not demonstrate that fibrinogen complexed with the antigenic site of the dextran molecule. Electrophoresis verified these experiments, but chemical determinations continued to show a marked increase in serum fibrinogen concentration in animals infused with dextran. The site of bonding of the fibrinogen molecule was not demonstrated even though such bonding seems to occur.

These experiments were not done to prove or disprove the usefulness of dextran as a plasma expander; however, the inaccuracy of fibrinogen determinations immediately following dextran infusion was verified.

D. Pulmonary Microembolism Associated with Transfusion:

Pulmonary microembolism of microaggregates associated with massive blood transfusion may be a cause of post-traumatic pulmonary embolism.

1. Effect of Micropore Filters: The purpose of this study was to investigate in the dog the influence on certain physiologic parameters of transfusion of blood containing platelet: white blood cell: fibrin (PWF) aggregates and to evaluate the effects of using blood transfusion filters of varying pore sizes during such transfusions. Exchange transfusions of approximately twice blood volume were performed in three groups of animals. Screen filtration pressure measurements verified the presence of large numbers of PWF aggregates in the transfusions. When

no transfusion filters or standard commercially available blood transfusion filters of pore size 170 μ were used, experimental animals developed pulmonary hypertension, a decrease in total body O_2 consumption, and metabolic acidosis. Interposition of Dacron wool (Swank) blood transfusion filters prevented these changes.

2. Pathophysiologic Changes Caused by Microemboli: The purpose of this study was to define in detail the pulmonary abnormalities that develop following transfusion of blood with an elevated SFP through standard blood transfusion filters. Exchange transfusions of approximately twice blood volume were administered through standard commercially available blood transfusion filters (measured pore size -- 200 microns) to 6 animals. SFP measurements verified the presence of large numbers of aggregates in the transfusions. Although filters reduced SFP of the stored blood somewhat, numerous microaggregates passed the filters, and post-filtration SFP remained high. After transfusion average O_2 consumption decreased to 77% of normal and metabolic acidosis developed. Pulmonary arterial hypertension was associated with an increase in pulmonary shunting of blood and a decrease in pulmonary diffusing capacity. The presence of extensive numbers of microemboli in the pulmonary arteriolar and capillary bed was confirmed by microscopic examination of lung tissue.

3. Recovery of Pulmonary Function: It was the purpose of this research to define the progression over several days of changes in pulmonary function and structure and to document the phases of recovery following transfusions to dogs of sublethal quantities of stored blood containing microaggregates. Ten dogs underwent partial exchange transfusions averaging 60% of blood volume through standard blood transfusion filters. Average screen filtration pressure (SFP) of the blood was 85 mm Hg. Pulmonary hypertension did not develop, but there were striking decreases in O_2 consumption, increases in Q_s/Q_t and decreases in Do_2. Changes became progressively more marked over the first 48 to 72 hours after the transfusions. Pulmonary function of surviving animals returned nearly to normal by the sixth day after transfusions. Pathologic examinations of the lungs of animals sequentially sacrificed over 6 days showed intravascular microemboli, alveolar cell hyperplasia and interstitial and alveolar pulmonary edema. Progressive recovery was associated with progressive resolution of all detrimental changes. In 6 animals exchange transfused 100% of their blood volumes through Dacron wool (Swank) filters and in three control animals that were not transfused, there were no significant changes in pulmonary function or structure. These experiments define the progression of deterioration and recovery over 6 days of pulmonary function in dogs after sublethal pulmonary microembolism occurring during blood transfusion.

4. Pathologic Changes in Dogs: Dog lungs were studied by light and electron microscopy at intervals from 48 hours to six days following exchange transfusions of sublethal volumes of such microaggregate-rich blood through either standard or Dacron wool (Swank) transfusion filters.

After transfusion through standard filters, the pulmonary microvasculature was extensively occluded by microemboli. Swelling of capillary endothelial cells, interstitial and alveolar edema, and hypoxic changes in types I and II alveolar epithelial cells were noted. Changes then progressively resolved. These detrimental changes were prevented when microaggregates were removed by Dacron wool (Swank) filters.

Mechanical occlusion of the pulmonary vasculature probably plays a minor role in initiating the structural changes observed. Release of lysosomes from disintegrating microaggregates is believed to be the significant factor initiating a chain of events leading to progressive pulmonary damage.

5. Pulmonary Shunting in Humans After Transfusion: It was the purpose of this study to determine whether alterations in pulmonary shunting occur in humans following transfusion of stored blood through standard transfusion filters.

In eight patients transfused over 20% of blood volumes through standard filters, Q_s/Q_t and alveolar-arterial O_2 tension differences increased significantly. These changes did not occur in patients transfused comparable amounts of blood through Dacron wool (Swank) filters or in patients transfused less than 20% of blood volumes. A direct correlation was found between the absolute percent change in Q_s/Q_t and the quantity of microaggregates passing the filter and present in the transfused blood.

It is concluded that removal from stored blood of microaggregates by administration of the blood through effective micropore transfusion filters prevents an increase in Q_s/Q_t caused by administration of such material.

6. Various Micropore Filters:

a. Dacron wool (Swank) filter

Stored human blood of varying age was passed through standard commercial blood transfusion filters (pore size, 170μ) and Swank Dacron wool blood transfusion filters (pore size 20μ). Passage through the Dacron filter resulted in a marked decrease in SFP and an increase in filter weight indicating removal of microaggregates which have been implicated as a cause of pulmonary insufficiency. The commercial filter tested did not appear to be effective in removing these harmful aggregates. On the basis of this research it is concluded that the Swank Dacron wool blood transfusion filter will prevent pulmonary microemboli during transfusion. Because aggregate removal appeared to be quantitative, it is recommended that no more than four units of blood be passed through each Dacron wool filter.

b. Polyester mesh (Pall) filter

Stored human blood of varying age was passed through polyester mesh (Pall) micropore blood transfusion (pore size, 40 μ). Passage through the filter resulted in decreased screen filtration pressure (SFP) of the blood and increased filter weight. Numerous microaggregates were removed, but SFP did not return to normal after filtration.

On the basis of this research, we conclude that polyester mesh micropore blood transfusion filters are not as effective as Dacron wool (Swank) transfusion filters in removal of microaggregates from stored human blood. If a polyester mesh filter must be used, it is recommended that once occlusion of the filter has occurred, the filter should then be discarded and another inserted.

c. Comparison of Dacron wool (Swank) and polyester mesh (Pall) filters

Experiments were performed to compare the effectiveness in vivo of the two most widely used micropore blood transfusion filters in preventing detrimental physiologic changes associated with transfusion of microaggregate-containing blood. Exchange transfusion with stored blood having an elevated screen filtration pressure (SFP) through polyester mesh (Pall) filters (Group PM) was followed by decreases in arterial blood pH and O_2 consumption, increases in arterial blood pyruvate and lactate concentrations, and a decrease in pulmonary DO_2. The lungs of 5 of 6 animals revealed emboli far out in the pulmonary microcirculation. These changes did not occur in animals transfused through Dacron wool (Swank) filters (Group DW). Even though an increase after transfusion in pulmonary Q_s/Q_t in Group PM did not achieve statistical significance when compared to pretransfusion Q_s/Q_t, it was significantly higher than that in animals in Group DW. Both filters removed considerable quantities of microaggregates; however, the polyester mesh (Pall) filters permitted passage of small microaggregates and development of detrimental physiologic changes. Dacron wool (Swank) filters completely removed measurable microaggregates and detrimental changes did not occur.

d. Polyurethane foam (Bentley) filter

Stored human blood of varying age was passed through polyurethane foam (Bentley) micropore blood transfusion filters. Passage through these filters resulted in decreased screen filtration pressure (SFP) of the blood and increased filter weights. Numerous microaggregates were removed and SFP returned to normal after filtration. Occlusion of the filter occurred after passage of only 2 units of whole blood.

On the basis of this research, we conclude that polyurethane foam (Bentley) micropore blood transfusion filters are effective in removal of microaggregates from stored human blood. Because the filtering capacity is not great, it is recommended that when these filters are used during transfusion a new filter be used for each unit of blood administered.

e. Dual mode (Johnson & Johnson) filter

Stored human whole blood and red blood cells of varying age were passed through dual mode micropore blood transfusion filters. Passage through the filters resulted in markedly decreased screen filtration pressure (SFP) of the blood and increased filter weights. Numerous microaggregates were removed and SFP returned to normal. Filtration resulted in reduced platelet and white cell counts but other blood components were not adversely affected. On the basis of this research, we conclude that this micropore blood transfusion filter is effective in removing microaggregates from stored whole blood and red blood cells. It has a high capacity and rapid flow rate and is reliable during pressure transfusion.

f. Polyester fiber (Fenwal II) filter

The filtration characteristics of a new polyester fiber (Fenwal II) micropore blood transfusion filter were investigated. Filtration of stored human whole blood and packed cells resulted in return of screen filtration pressure (SFP) of the blood to normal. Increased filter weights verified removal of large amounts of debris and microaggregates from the blood. Filtration of large quantities of blood accomplished at very high flow rates did not adversely affect the composition of the filtered blood. We conclude that the polyester fiber (Fenwal II) micropore blood transfusion filter is effective in removing microaggregates from stored whole blood and packed cells. It has a high volume capacity, allows rapid flow, and is reliable during pressure transfusion.

7. Microaggregates in Stored Blood: Experiments were performed to compare the formation of microaggregates in stored human whole blood (WB) with that in stored packed cells (PC) and also to compare the effectiveness of standard blood transfusion filters with Dacron wool (Swank) micropore transfusion filters in removing such microaggregates. After 5, 10, 15 and 20 days of storage SFP and debris weights of PC's were considerably greater than those of matched WB samples. Passage of either WB or PC's through standard blood transfusion filters resulted in small decreases in SFP and debris weights. Passage of either WB or PC's through Dacron wool (Swank) transfusion filters led to striking and highly significant decreases in both SFP and debris weights. When stored PC's were diluted to the same hematocrits as their corresponding WB samples, SFP

remained considerably elevated above those of the WB samples. On the basis of this research, it is concluded that centrifugation of blood during component separation leads to a significant increase in microaggregate formation over and above that which progressively occurs during storage and that the risk of pulmonary microembolization during transfusion with stored PC's is greater than that during WB transfusion. For this reason, Dacron wool (Swank) filters should always be used when PC's are being transfused.

8. Prevention of Microaggregate Formation in Stored Whole Blood and Packed Cells: Dextran-40 (D-40) is known to have a specific disaggregation effect on aggregated platelets. It is also known that microaggregates of white cells and platelets occur in stored human blood. Such microaggregates have been shown to have a detrimental pulmonary effect when transfused into animal and man. It was the purpose of this investigation to determine the effects of D-40 on the prevention and resolution of microaggregates in stored human whole blood (WB) and packed cells (PC).

Blood was obtained from human donors at the Charity Hospital of Louisiana blood donor station. Collection and storage methods were those standard to this institution. Each unit of blood was divided into two equal parts immediately after collection. One part was stored as WB and the other as PC.

10% D-40 and normal saline was added to both WB and PC samples. A total of 37 units were used in each study.

A total of 16 units of PC were included in each study group. Average age of the samples was 12.6 days. SFP of the untreated PC samples was 325 mm. When D-40 had been added, SFP was reduced considerably to 195 mm. When only saline was added, SFP was 270 mm.

When D-40 was added after PC had been stored for 12.6 days, there appeared to be no effect on resolution of aggregates which had already formed.

From this study it appears that D-40 has little or no effect on already formed microaggregates in stored PC. However, microaggregate formation when D-40 has been added initially to the storage solution was considerably decreased ($p<0.01$).

E. Retrospective Clinical Studies:

1. Morbidity and Mortality Associated with Flail Chest Injury: Patients with severe flail chest injuries are difficult to manage and have a relatively high mortality rate. Introduction of modern forms of mechanical ventilation has greatly simplified the care of such patients.

Mechanical ventilation also appears to have led to a significant reduction in their mortality; however, this has not been firmly documented and mechanical ventilation has been shown to be associated with a high incidence of complications.

Remarkably few data have become available since this form of treatment became widespread which define the causes of morbidity and mortality specifically in patients with flail chest injuries. In this study a retrospective review of patients admitted with flail chest injury was done to determine causes of morbidity and mortality in such patients.

The records of patients with severe flail chests who were admitted to Charity Hospital of Louisiana during the five year period from 1965 through 1969 were reviewed. All had a tracheotomy and only two did not receive mechanical ventilatory assistance. All who died underwent postmortem examinations.

Of the 85 patients studied, automobile accidents led to the injuries in 81 (96%) and 30 (35%) died. There was no significant statistical relation between survival or death and sex, age or anatomical location of the flail segment. Bronchopneumonia and/or tracheobronchitis occurred in 74 (87%) of the patients and pulmonary infection accounted for 9 (30%) of the deaths.

Acute bronchopneumonia led to the deaths of 7 (37%) of the 19 patients with craniocerebral injuries who died; but caused the deaths of only 2 (18%) of the 11 patients without craniocerebral injuries who died. Aspiration pneumonitis caused the deaths of 3 (16%) of the patients with craniocerebral injuries, but did not occur in any patient without craniocerebral injuries.

Blunt abdominal trauma occurred in 26 patients. Of these, 5 (20%) died as a direct result of their injury. In the remaining 21 patients, all of whom underwent surgical exploration, ruptured spleens, liver lacerations, retroperitoneal hematomas, or combinations of these were found in 19 (73%).

It is remarkable that in spite of notable advances made in all areas of medical knowledge and care during the years 1947 - 1969 mortality for patients with severe flail chest injuries in this series remained essentially the same as that in other earlier reported series. Since completion of this study, adequate early consideration of multiple system injury and delicate purposeful therapy by a team of medical personnel well-trained in multiple disciplines has aided greatly in overcoming this problem.

2. Gunshot Wounds of the Abdomen: Whether or not all patients with penetrating abdominal wounds should undergo surgical exploration has

been the subject of several studies. Some have stressed the conservative approach to abdominal stab wounds if no clinical signs of intraperitoneal injury are present. This sort of expectant therapy for GSWs to the abdomen has also been reported by Ryzoff et al, (Surg., 59:650, 1966) Shaftan (J. Med. Soc. N.Y., 68:653, 1971) and Nance et al, (Ann. Surg., 179:639, 1974). Close observation of patients with abdominal stab wounds when there are no signs of intra-abdominal injury may well be justifiable, and morbidity in this condition has noticeably decreased, especially when certain diagnostic procedures such as peritoneal lavage, intravenous pyelography, and arteriography have been performed when indicated.

Others, however, favor exploration of all penetrating wounds to the abdomen, especially for GSWs. The purpose of this study was to determine whether exploration of all penetrating abdominal gunshot wounds is preferable to conservative management.

During a five-year period at Charity Hospital from July 1968 through June 1973, 277 abdominal gunshot wounds (GSWs) occurred, the overall fatality of which was 10%.

Abdominal exploration was done in all patients. No intra-abdominal injury was found in 40 patients (14%) and no death occurred in this group. There were 28 fatalities (12%) in 237 patients (86%) who had intra-abdominal injuries. Morbidity and mortality were related not only to the number of organs injured, but also to specific organs injured. The leading cause of early death was hypovolemia due to major vessel injuries. Septicemia was the most common cause of death if the patient survived the first 24 hours of hospitalization.

Penetrating abdominal stab wounds and gunshot wounds must be considered separately, and mandatory routine abdominal exploration for all penetrating gunshot wounds is advised. In stab wounds to the abdomen, conservative management may be preferable.

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